REMARKS

I. Preliminary Remarks

Claims 30-59 are pending in the Application. Claims 1-29 are canceled. Claims 35 and 37 are allowed. Claims 30, 32-34, 36, 38-59 are rejected. Claim 31 is objected to. Claims 30-34, 36, 38-39, 42-49, and 54-57 are amended herein. Claims 60-76 are new. The amendments are made for clarity, and support for these changes is found throughout the specification. The amendments do not include new matter. Reconsideration and withdrawal of the rejections and objections are solicited for the reasons set out below. Amendments to the specification are made to correct a clerical error. This response is timely filed without the need for an extension of time. However, if the Office determines that a fee for an extension or another matter is required, please charge Account No. 21-0718.

II. Amendment to the Specification.

The specification required correction because of the incorrect recitation of US Serial Number 08/107,908. The Examiner determined that "08/107,908" was an inadvertent typo and the incorporation of US Patent Nos. 6,168, 942; 6,410,032; and 6,410,299 does not present new matter.

In the specification, page 13 lines 16-20 and page 15 lines 6-13 have been amended to recite US Patent Nos. 6,168, 942; 6,410,032; and 6,410,299 which claim the benefit of US Application Serial No. 60/107,908. Thus, the requirement to amend the typo throughout the specification has been met.

III. Patentability Arguments

A. The Objection to Claims 32, 34, 38, 43, 45, and 49 May Properly Be Withdrawn.

Claims 32, 34, 38, 43, 45, and 49 were objected to because they lack periods. Claims 32, 34, 38, 43, and 45 have been amended to include periods (See listing of claims above). Claim 49 included a period as previously filed. Thus, the objection of these claims is overcome. Withdrawal of the objection is therefore respectfully requested.

B. The Indefiniteness Rejections of Claims 30, 32-34, 36, and 38-59 under 35 U.S.C. §112, Second Paragraph, May Properly Be Withdrawn.

The Examiner rejected claims 30, 32-34, 36, and 38-59 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Applicants respectfully traverse this rejection.

The Examiner states that claims 30, 32-34, and 42-45 are not clear for reciting the phrase "at least about" and that this rejection also affects all dependent claims. Applicants have deleted the word "about" from these claims, thus rendering this rejection moot. Applicants request withdrawal of this rejection.

The Examiner states that "these same claims are also rejected because it cannot be determined from the language recited how N^{pro} is mutated since at least 36 or 310 base pairs of the 5' region remains intact. This language encompasses the entire, intact N^{pro} gene." However, The N^{pro} coding region has 504 base pairs (page 7, lines 20-21), and the mutation is described in detail on page 5 line 24 through page 7 line 8 of the specification. In particular, it is stated (page 5, line 30) "BVDV constructs which maintain at least a portion of the 5' sequence of the coding region exhibit an increased efficiency in the translation of viral polyprotein precursors as compared to BVDdN1, and the viruses derived from such constructs replicate more efficiently that BVDdN1" and (page 7, line 3) According to the present invention, the mutation is sufficient to inactivate the function of the N^{pro} protein so as to keep the virus attenuated, and leaves the 5' region of the N^{pro} gene intact so as to achieve a desirable rate of viral replication." Applicants request withdrawal of this rejection.

Examiner states there is a lack of antecedent basis in claim 36 regarding the dependency from claim 37, and that claim 36 depends from itself. This rejection also affects claims 38-41. Applicants have amended the claims to correct the lack of antecedent basis and the incorrect dependency in claim 36, which renders this rejection moot. Applicants request withdrawal of this rejection.

Examiner states there is a lack of antecedent basis in claims 38, 47, 49, 55, and 57 regarding dependency from claim 36 and 37. This rejection also affects claims 40, 51, and 52.

Applicants have amended the claims to correct the lack of antecedent basis, which renders this rejection moot. Applicants request withdrawal of this rejection.

In summary, for the foregoing reasons, Applicants respectfully submit that the rejection of claims claims 30, 32-34, 36, and 38-59 for indefiniteness under 35 U.S.C. §112, second paragraph, may be properly withdrawn. Applicants respectfully requests withdrawal of this rejection.

C. The Enablement Rejection of Claims 30-34, 36, and 38-59 under 35 U.S.C. §112, First Paragraph, May Properly Be Withdrawn.

Claims 30-34, 36, and 38-59 were rejected under 35 U.S.C. §112, First Paragraph, "because the specification, while being enabling for an attenuated BVDV that has about 310 base pairs of the N^{pro} gene intact, does not reasonable provide enablement for scope of mutations to Npro claimed or an intact N^{pro}." The Examiner states that "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." Applicants respectfully traverse this rejection.

Applicants respectfully submit that a specification only needs to "supply the novel aspects of an invention in order to constitute adequate enablement." Genentech, Inc. v. Novo Nordisk. 108 F.3d 1361,1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), cert, denied. 522 U.S. 963 (1997) (emphasis added). The omission of minor details does not cause a specification to fail to meet the enablement requirement. Id. The present invention relates to attenuated forms of bovine viral diarrhea (BVD) viruses. In particular the present invention relates to attenuated BVD viruses made by mutating the N^{pro} protease gene and inserting a bovine ubiquitin coding sequence. The claims do not encompass an intact N^{pro} gene. A novel aspect of the invention is found in claim 30, which provides for an attenuated bovine viral diarrhea virus wherein said virus carries in the viral genome: (a) a mutated N^{pro} coding sequence comprising an intact 5' region of at lease 36 base pairs, wherein said mutated N^{pro} coding sequence encodes an inactive N^{pro} protein; and (b) a sequence coding for a monomeric bovine ubiquitin wherein the ubiquitin coding sequence is operably placed between the 3' end of said mutated N^{pro} coding sequence and the 5' end of the coding sequence for the viral core protein. In this regard, Applicants submit that the specification

provides sufficient guidance and working examples relating to this novel aspect. The claim clearly defines what is covered.

Applicants recognize that those skilled in the art may conduct additional experimentation in order to inactivate the N^{pro} gene and screen for mutations according to the invention. However, Applicants respectfully submit that such experimentation is not undue and can be achieved by one skilled in the art following routine procedures as outlined in the specification (see page 10, lines 9-20) and US patent Nos. 6,168,942; 6,410,031; and 6,410,299, which have been incorporated by reference. Applicants have specified a small area of genome to be modified (see page 10, lines 5-8), and included a functional limitation.

Examiner states that "the claims fail to define a structure of the intact N^{pro} gene that remains in the attenuated BVDV genome... While the claims encompass the entire, intact N^{pro} gene, the claims also require that N^{pro} be mutated to produce an attenuated BVDV." The Applicants are, in part (see claim 30), claiming virus, and they are claiming said virus comprising a mutation in a nucleotide sequence with a specific structure: function relationship in the claims. These claims are drawn to an organism (virus) comprising a genetic modification at a particular locus (gene), providing a specified change of phenotype. There is support in the specification for a defined function, N^{pro} biological activity. It is found on page 5, line 26 through page 6, line 8. The specification there also describes the result of a mutation in the N^{pro} gene at the location described in the claims.

Applicants define the amino acid sequence in the claimed virus by a combination of structural (claim 30: a mutated N^{pro} coding sequence comprising an intact 5' region of at lease 36 base pairs; and a sequence coding for a monomeric bovine ubiquitin wherein the ubiquitin coding sequence is operably placed between the 3' end of said mutated N^{pro} coding sequence and the 5' end of the coding sequence for the viral core protein) and functional properties (wherein said mutated N^{pro} coding sequence encodes an inactive N^{pro} protein). The decreased N^{pro} biological activity attenuates the virus. Thus, the claimed invention meets the requirements of "Product by Function" set forth in Example 14 of the "Revised Interim Written Description Guidelines" published by the Patent Office.

The Applicants do not need to specifically point out where the mutation is located within the N^{pro} sequence, as long as the mutation disrupts the expression or function of the encoded N^{pro}

polypeptide. In claims to transgenic animals comprising a "knockout" of a particular endogenous gene, the claims are not limited to the specific site of disruption within the sequence or the sequence identification number disclosed, see e.g., U.S. Patent Nos.: 5,714,667; 5,777,195; 6,087,555; and 6,100,445. The presently claimed attenuated viruses are analogous to knockout animals having a particular phenotype because the patents at issue do not describe the sequence of every homolog of the gene of every mouse within the scope of the issued claims. The claimed attenuated virus recites a combination of functional and structural properties. The claimed virus comprises a mutation in a polynucleotide encoding N^{pro}, which results in the disrupted function of N^{pro} activity, resulting in attenuation. The specification provides adequate written descriptive support for mutating an N^{pro} polypeptide to result in attenuation of virus.

The Examiner states that "While it is agreed that every enabled embodiment need not be described to support the claims, the disclosure must provide some guidance to the skilled artisan to practice the invention claimed. The disclosure has disclosed two species of attenuated BVDV that have an Npro gene with an intact 5' end. There is no discussion present in the specification or the art regarding the remaining residues of the Npro gene or what effect any of residues would have on attenuating phenotype or gene inactivation if any one or any combination were substituted, deleted, inserted or remained intact. Without some guidance, the skilled artisan would be unable to predict which nucleic acids within the 3'end of the Npro gene have an effect with respect to its function and subsequent virus attenuation, which are required elements recited in the claims." However, as stated in a previous response, the specification makes it clear that the region to be mutated is the 3' end of the N^{pro} protease gene. US Patents 6,168,942; 6,410,032, and 6,410,299 make it clear that a mutated N^{pro} protease gene does result in an attenuated phenotype, and that one of ordinary skill when faced with the problem of inactivating N^{pro} is quite able to predict and screen mutations which are likely to result in an inactive gene.

Applicants submit that arguments similar to those above apply to Claims 31-34, 36, and 38-59. In view of the foregoing, Applicants respectfully submit that one skilled in the art can practice the claimed invention without undue experimentation. Thus, the rejection of Claims 30-34, 36, and 38-59 under 35 U.S.C. 112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

D. The Obviousness Rejection of Claims 30, 33, 36, 38-42, 44, 46, 47, 54, and 55 under 35 U.S.C. §103(a) May Be Properly Withdrawn.

Claims 30, 33, 36, 38-42, 44, 46, 47, 54 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Behrens et al. (Journal of Virology. 1998; 72 (3): 2364-372). Applicants respectfully traverse this rejection.

As stated in the MPEP (§2141), to support an obviousness rejection, four basic criteria must be met. These are (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined. Clearly for prior art to render an invention obvious, it must render obvious the whole invention and not merely some part of the invention (*In re Antonie* 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1997)). The prior art must also be considered as a whole including parts that teach away from Applicant's invention. Applicant respectfully submits that these criteria are not met in the Examiner's rejections.

Behrens describes a mutated BVDV with an intact 5' region of 126 base pairs, but does not describe a utility of the virus. Behrens does not describe using a bovine ubiquitin, which the instant case does (page 6, line 1-8), and Behrens does not describe constructing a BVD mutant with at least 36 or 310 intact base pairs at the 5' end. In addition, Behrens does not describe using the attenuated virus for immunogenic compositions, vaccine compositions, inducing an immune response against bovine viral diarrhea virus, or treating bovine viral diarrhea virus infections. As stated above, for art to render an invention obvious, it must render obvious the whole invention and not merely some part of the invention. For example, in re Papesch (137 USPQ 43) held:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify

a plot of land the thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.

The argument has been made that patentability is here being asserted only on the basis of one property, the anti-inflammatory activity, and that the compounds claimed and the compound of the prior art presumably have many properties in common. Presumably they do, but presumption is all we have here. The same is true of all of the compounds of the above cases which were held patentable over compounds of the prior art, many of which must have had more in common by way of properties than the compounds here because the relationships, structurally, were even closer than here.

In the present case, Applicants teach using a bovine ubiquitin, constructing BVD mutants comprising an intact 5' region of at least 36 or 310 base pairs, and using the attenuated virus for immunogenic compositions, vaccine compositions, inducing an immune response against bovine viral diarrhea virus, or treating bovine viral diarrhea virus infections. Behrens describes a mutated BVDV with an intact 5' region of 126 base pairs, but does not describe a utility of the virus. As stated in *in re Larsen* 130 USPQ 209 at 210, "Since there was nothing to indicate that the compounds, when made, would have these properties, it was not obvious to make the compounds." To apply the holding of Larsen to the present facts, we could conclude: Since there was nothing in Behrens that describes making a mutated BVD virus comprising an intact 5' end of at least 36 or 310 base pairs or using the attenuated virus for immunogenic compositions, vaccine compositions, inducing an immune response against bovine viral diarrhea virus, or treating bovine viral diarrhea virus infections, it was not obvious to make Applicants' mutants or to use them for these purposes.

Based on the arguments presented above, Applicants respectfully submit that the rejection of claims 30, 33, 36, 38-42, 44, 46, 47, 54 and 55 under 35 USC 103(a) may be properly withdrawn. Applicant respectfully requests withdrawal of this rejection.

E. Allowable Subject Matter.

Examiner stated that Claim 31 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants have amended claim 31 as shown in the listing of claims, which renders this objection moot. Applicants respectfully request withdrawal of this objection.

IV. Conclusion.

In view of the amendments and remarks made herein, Applicants respectfully submit that Claims 30 to 76 are in condition for allowance and request expedited notification of same.

Respectfully submitted,

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